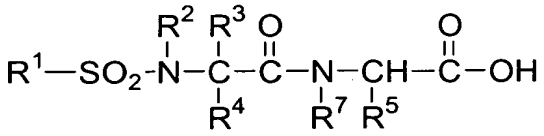
Rejection of Claims as Being Drawn to an Improper Markush Group

Claims 1-4, 6-7, 10 and 12-18 stand rejected as being drawn to an improper Markush group. The Examiner states that the deletion of non-elected subject matter from the pending claims would obviate this rejection. Applicants have amended the claims in accordance with the Examiner's suggestion.

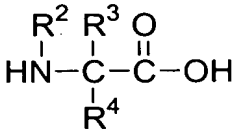
Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1-4, 6-7, 10, 12-13 and 15-18 stand rejected as being not enabled. The Examiner raises two enablement issues: 1) that the specification does not enable one to prepare compounds commensurate with claim scope; and, 2) that the specification does not enable one to use the compounds as therapeutic agents without undue experimentation. Applicants respectfully disagree with the Examiner's position on both issues.

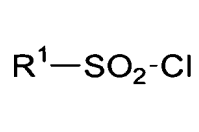
First, Applicants provide a detailed synthetic route on pages 56 to 62 of the specification. For instance, in a preferred method of synthesis, compounds of the structure



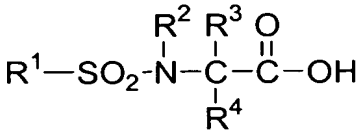
are made by coupling an amino acid of formula II (p. 56) with a sulfonyl chloride of formula III (p. 57) to provide an N-sulfonyl amino acid of formula IV (p. 57). Coupling of IV with amino acid derivative VI (p. 60) provides the desired compound.



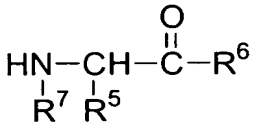
(II)



(III)



(IV)

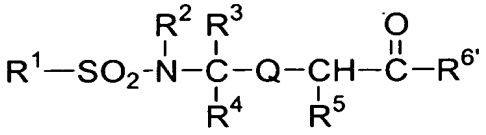


(VI)

The specification provides a long list of formula II amino acids that can be employed in the synthetic route (p. 57, line 29 to p. 58, line 18). The list includes L-proline and L-proline derivatives (R^2 and R^3 form a 5-membered heterocycle containing 1 nitrogen), L-pipecolinic acid (R^2 and R^3 form a 6-membered heterocycle containing 1 nitrogen), L-azetidine-2-carboxylic acid (R^2 and R^3 form a 4-membered heterocycle containing 1 nitrogen), L-thiazolidine-4-carboxylic acid (R^2 and R^3 form a 5-membered heterocycle containing 1 sulfur and 1 nitrogen) as well as other amino acids where R^2 and R^3 form a heterocycle.

The specification includes a synthetic route to the claimed compounds that one of ordinary skill in the art could readily follow. It further provides the necessary reactants for synthesizing compounds containing a wide variety of heterocyclic structures. Applicants respectfully submit, therefore, that the claim scope is enabled as to making the presently claimed invention.

As to the second issue, Applicants have presented biological data on over 50 compounds embraced by the following formula (pages 99-115 for compounds; page 117 for report of activity):



The tested compounds represent a wide variety of structures. R^3 and R^4, for instance, are alkyl or cycloalkyl, such as cyclopentyl, cyclohexyl, cyclobutyl, cyclopropyl. R^5 is shown to be an array of different benzylic substituents. R^2 is alkyl or a portion of a pyrrolic ring. Each of these compounds has an IC_{50} of 15 μM or less in an *in vitro* VLA-4 binding assay (pages 116-117).

To satisfy the enablement requirement, one does not have to provide experimental results on each and every imagined subgenus of a generic structure. "[T]he scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." MPEP 2164.08 citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants have provided data on over 50 diverse compounds to support the presently claimed invention. The presented diversity reasonably correlates with the scope of the generic structure. Respectfully, therefore, Applicants request the withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claims 1-4, 6-7, 10 and 12-18 stand rejected as being indefinite. The Examiner points to eleven different issues in support of his finding. These points are discussed below.

Definition of "Aryl": The Examiner states that the definition of "aryl" represents a distortion in an art recognized term. Applicants respectfully disagree. As defined in the present application, "aryl" includes a carbocyclic, aromatic ring that may or may not be fused to one or more other rings. The other rings may be aromatic or nonaromatic. Rather than distorting the art recognized definition of "aryl," the definition focuses on a common, structural element of a class of compounds. Applicants submit that one of ordinary skill in the art would readily grasp this focus and would appreciate the scope of any claim including the term. Respectfully, therefore, use of this term in a claim does not render it indefinite.

"Heterocyclic" and "Heteroaryl": The Examiner states that claims reciting both "heterocyclic" and "heteroaryl" are indefinite. In support of his argument, the Examiner

cites case law regarding the inclusion of "exemplary" language in a claim (*e.g.*, "R is halogen, for example, chlorine," MPEP 2173.05(d)). Applicants respectfully submit that cited case law was not intended to cover the present issue. The inclusion of exemplary language in a claim creates confusion, since one does not know whether the broad class (*e.g.*, halogen) or the narrow example (*e.g.*, chlorine) defines the claim boundaries. The inclusion of two terms in a Markush group that have overlapping definitions does not provide ambiguity as to the metes and bounds of a claim. The essence of a Markush group is alternative expression. MPEP 2173.05(h). The MPEP even addresses the case where a compound may be embraced by more than one member of a Markush group: "For example, the Markush group, 'selected from the group consisting of amino, halogen, nitro, chloro and alkly' should be acceptable even though 'halogen' is generic to 'chloro.'" *Id.* As the MPEP clearly states that such a Markush group is acceptable, Applicants submit that claims including both "heterocyclic" and "heteroaryl" are not indefinite.

*"A compound .... **and** pharmaceutically acceptable salt thereof..."*: The Examiner stated that the use of "and" rather than "or" in the preceding phrase renders claims 1 and 2 indefinite. Applicants have amended claims 1 and 2 to recite "or" rather than "and."

Definitions of Y and Z: The Examiner stated that the use of "and" in the definitions of Y and Z rather than "or" renders claim 2 indefinite. Applicants have amended claim 2 to recite "or" rather than "and" in the definitions of Y and Z.

The Symbol "ϕ": The Examiner stated that the use of the symbol "ϕ" in claims 12 and 13 renders the claims indefinite. According to the Examiner, there is no explanation of the symbol, and the group phenyl is dually represented by the symbol and the term "phenyl." Applicants respectfully request clarification on this issue from the Examiner. The symbol "ϕ" is an art recognized symbol for "phenyl." The Examiner supports this point when he discusses "dual representation" of the group phenyl in claims 12 and 13. Furthermore, "ϕ" is simply the symbol for "phenyl." One is formulaic and the other is

alphabetic. Applicants respectfully submit that one of ordinary skill is not confused by the use of both formulaic and alphabetic representations of the same term. Applicants are, however, prepared to replace the symbol "ϕ" with the word "phenyl" in the subject claims, if the Examiner does not find the present argument persuasive.

*"A compound ... **and** pharmaceutically acceptable salt thereof"*: The Examiner stated that the use of "and" rather than "or" in the preceding phrase renders claim 14 indefinite. Applicants have amended claim 14 to recite "or" rather than "and."

Recitation of "as well as any of the ester....": The Examiner stated that claim 14 is unclear due to a clause starting with "as well as any of the ester...." Applicants have canceled Claim 14, but note that new Claim 22 recites the following: "as well as any of the ester compounds recited above wherein one ester group is replaced with another ester group selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester." This clause clearly means that when a methyl ester is recited (*e.g.*, *N*-toluene-4-sulfonyl)-L-α-methylprolyl-L-4-(isonicotinamido)phenylalanine methyl ester), the methyl ester group is interchangeable with an ethyl ester group (*i.e.*, *N*-toluene-4-sulfonyl)-L-α-methylprolyl-L-4-(isonicotinamido)phenylalanine ethyl ester), an *n*-propyl ester group (*i.e.*, *N*-toluene-4-sulfonyl)-L-α-methylprolyl-L-4-(isonicotinamido)phenylalanine *n*-propyl ester), an isopropyl ester group (*i.e.*, *N*-toluene-4-sulfonyl)-L-α-methylprolyl-L-4-(isonicotinamido)phenylalanine isopropyl ester), etc. Applicants respectfully contend that the clause of Claim 22 does not render it indefinite.

Variable "$R^{6'}$": The Examiner states that variable "$R^{6'}$" in claim 16 is not defined in the claim. Applicants have amended claim 16 such that the structure contains the substituent "R^6" rather than "$R^{6'}$." Support for this amendment can be found, for example, at page 7, lines 25-30 and at page 9, lines 3-13 of the instant application.

The phrase "diabetes (including acute juvenile onset diabetes)": The Examiner states that phrases beginning with the word "including" render claim 18 indefinite. Applicants have amended claim 18 to delete the referenced phrases. Claims 19 and 20, which are directed to juvenile onset diabetes and ulcerative colitis and Crohn's disease respectively, have been added.

The phrase "other cerebral traumas": The Examiner states that the phrase "other cerebral traumas" is unclear in claim 18. As originally written, stroke is an example of a cerebral trauma. Applicants have deleted the recitation to "stroke" and "other" in claim 18. Claim 21, which is directed to stroke, has been added.

Alzheimer's as Inflammatory Disease: The Examiner states that it is unclear how "Alzheimer's disease" is recited under inflammatory disease. Applicants submit that by the time the instant application was filed, inflammatory mechanisms were implicated in the etiology of Alzheimer's. Courtesy copies of the following articles which discuss such mechanisms have been enclosed with this response: *Neurodegeneration* (1996) 5(4): 497-503; and, *Gerontology* (1997) 43(1-2): 143-149. Applicants respectfully contend that these articles support the inclusion of Alzheimer's as an inflammatory disease.

Rejection of Claims Under 35 U.S.C. 103 (JP 4,154,732)

Claims 1-3, 6-7, 10, 12-13 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over JP 4,154,732. The Examiner states that the reference discloses a group of prolinyl derivatives that differ from the presently claimed compounds by virtue of a methylene (*i.e.*, CH_2) group. He further states that the presently claimed compounds are *prima facie* obvious over the reference because they are structurally homologous. Applicants respectfully contend that a *prima facie* case of obviousness has not been made.

There is substantial case law regarding structural similarity and a *prima facie* case of obviousness. The MPEP crystallizes this line of cases into a single sentence: "A *prima facie* case of obviousness may be made when chemical compounds have very close

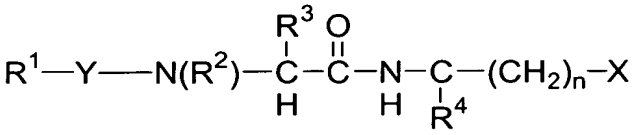
structural similarities and similar utilities." MPEP 2144.09. The prolinyl derivatives discussed in JP 4,154,732 are resolving agents for the optical resolution of racemic amines. That is a far cry from therapeutic and diagnostic applications discussed in the instant application. In short, one of ordinary skill would not be motivated to modify a resolving agent to arrive at a compound that binds VLA-4. Applicants respectfully request, therefore, that the obviousness rejection over JP 4,154,732 be withdrawn.

Rejection of Claims Under 35 U.S.C. 103 (WO 96/22966)

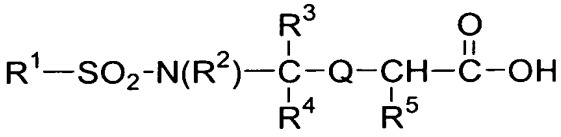
Claims 1-3, 6-7, 10, and 12-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/22966. The Examiner states that the presently claimed compounds are *prima facie* obvious over the reference because they are structurally homologous to the generic group. Applicants respectfully contend that a *prima facie* case of obviousness has not been made.

Applicants are confused by the Examiner's characterization of WO 96/22966. The Examiner first states that the reference discloses a generic group of compounds embracing Applicants' presently claimed compounds and then states that the generic group differs from the claimed compounds by a methylene (*i.e.*, CH_2) group. Clearly, both of these statements cannot be true.

Applicants contend that the generic group of WO 96/22966 does not embrace the presently claimed compounds. Formula I of WO 96/22966 along with formula I of the instant application are shown below:



(I, WO 96/22966)



(I, instant application)

For formula I of the instant application, neither R^3 nor R^4 is hydrogen. This clearly excludes the presently claimed compounds from formula I of WO 96/22966.

The Examiner's rejection seems modeled after MPEP 2144.08, the section on "Genus-Species Guidelines." Where there is not a genus-species relationship or a genus-subgenus relationship, one should not rely upon those guidelines. Such a relationship does not exist in the instant case.

Furthermore, WO 96/22966 teaches away from the presently claimed compounds. The reference defines its most preferred compounds on page 36, lines 3-17. Each of the listed compounds contains a "Y" group that is equal to "C(O)" (reference to formula I above). This is a clear departure from Applicants' invention, which contains an "SO_2" group at the left hand portion of its formula I. Viewing WO 96/22966, therefore, one of ordinary skill would not be motivated to select substituents for the generic structure that would provide compounds similar to the presently claimed invention.

As Applicants' invention and the generic structure of the cited reference do not overlap, and as the cited reference teaches away from the presently claimed compounds, Applicants respectfully request that the obviousness rejection over WO 96/22966 be withdrawn.

Provisional Rejection Under Obviousness-Type Double Patenting

Claims 1-4, 6-7, 10 and 12-18 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 09/126,095. As this is a provisional rejection, it is not necessary for Applicants to traverse, obviate or render moot the rejection. Applicants do note, however, their disagreement with the Examiner's provisional finding.

Information Disclosure Statement

The Examiner did not consider a number of references cited by Applicants in an Information Disclosure Statement filed March 29, 1999. Applicants respectfully contend that this action was in error. Each of the crossed-off documents is a priority document for a published international patent application. Applicants clearly pointed out the relationship

between the international patent applications, which were also cited, and the crossed-off documents in the March 29, 1999 Information Disclosure Statement.

Furthermore, the Information Disclosure Statement filed by Applicants complied with the provisions of 37 CFR 1.97 and 1.98. According to the MPEP: "The Office has set forth the minimum requirements for information to be considered in 37 CFR 1.97 and 37 CFR 1.98. Once the minimum requirements have been met, the examiner has an obligation to consider the information." (MPEP 609, emphasis added.)

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the instant application is now in condition for allowance, and a notice to that effect is respectfully requested. In the event that a telephone conference could expedite prosecution of the instant application, the Examiner is encouraged to contact the undersigned attorney for Applicants.

Respectfully submitted,
Burns, Doane, Swecker & Mathis, L.L.P.

By: _____
Jeffrey A. McKinney
Reg. No. 43,795

P.O. Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300
Date: March 23, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph under the heading CROSS-REFERENCE TO RELATED APPLICATIONS has been amended as follows:

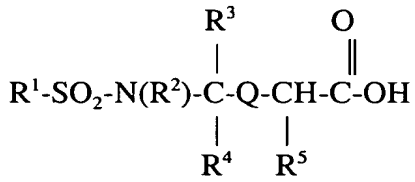
This application claims the benefit of U.S. Provisional Application No. [60/___,___] 60/108,164, which was converted pursuant to 37 C.F.R. § 1.53(c)(2)(i) from U.S. Patent Application No. 08/904,415, filed July 31, 1997, which application is incorporated herein by reference in its entirety.

The paragraph beginning on page 3, line 14 has been amended as follows:

VLA-4 (also referred to as $\alpha_4\beta_1$ integrin and CD49d/CD29), first identified by Hemler and Takada[1], is a member of the β1 integrin family of cell surface receptors, each of which comprises two subunits, an α chain and a β chain. VLA-4 contains an α4 chain and a β1 chain. There are at least nine β1 integrins, all sharing the same β1 chain and each having a distinct α chain. These nine receptors all bind a different complement of the various cell matrix molecules, such as fibronectin, laminin, and collagen. VLA-4, for example, binds to fibronectin. VLA-4 also binds non-matrix molecules that are expressed by endothelial and other cells. These non-matrix molecules include VCAM-1, which is expressed on cytokine-activated human umbilical vein endothelial cells in culture. Distinct epitopes of VLA-4 are responsible for the fibronectin and VCAM-1 binding activities and each activity has been shown to be inhibited independently.[2]

In the Claims:

1. (Amended) A compound of formula I:



I

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

[R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R^2 does not form a heterocyclic group with R^1,] R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 [can] form a heterocyclic or a substituted heterocyclic group;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl[, and, when R^3 does not form a heterocyclic group with R^2, then R^3 and R^4 together with the carbon atom to which they are attached can form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic group];

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl,

substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is =CH-X then (H) is removed from the formula and X is not hydroxyl;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

[and] or pharmaceutically acceptable salts thereof

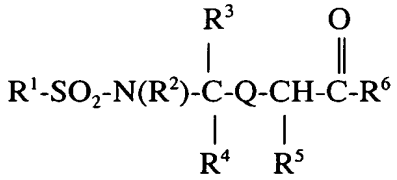
[with the provisos that

A. when R^1 and R^2 are joined together with the SO_2 and nitrogen atom to which they are attached respectively to form a benzoisothiazolone heterocyclic ring, R^3 is methyl, R^4 is methyl and Q is -C(O)NH- then R^5 is not benzyl;

B. when R^1 is *p*-methylphenyl, R^2 is hydrogen, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclohexyl, Q is -C(O)NH-, then R^5 is not benzyl; and

C. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl, Q is -C(O)N(CH_3)-, then R^5 is not benzyl].

2. (Amended) A compound of formula IA below:



IA

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

[R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and

R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R^2 does not form a heterocyclic group with R^1,] R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 [can] form a heterocyclic or a substituted heterocyclic group;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl [, and, when R^3 does not form a heterocyclic group with R^2, then R^3 and R^4 together with the carbon atom to which they are attached can form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic group];

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is $=CH-X$ then (H) is removed from the formula and X is not hydroxyl;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, [and] or substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic [and] or substituted heterocyclic;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

[and] or pharmaceutically acceptable salts thereof

with the [following provisos] proviso that

[A. when R^1 is *o*-carboxymethylphenyl, R^2 is hydrogen, R^3 is methyl, R^4 is methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

B. when R^1 and R^2 are joined to form a benzoisothiazolone heterocyclic ring, R^3 is methyl, R^4 is methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

C. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl or cyclohexyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not ethoxy;

D. when R^1 is benzyl, R^2, R^3 and R^4 are methyl, R^5 is *p*-hydroxybenzyl and Q is -C(O)NH-, then R^6 is not *t*-butoxy;

E. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl or cyclohexyl, R^5 is *p*-[*N,N*-(dimethylamino)carbonyloxy]benzyl and Q is -C(O)NH-, then R^6 is not *t*-butoxy;

F. when R^1 is benzyl, R^2, R^3 and R^4 are methyl, R^5 is *p*-[*N,N*-(dimethylamino)carbonyloxy]benzyl and Q is -C(O)NH-, then R^6 is not *t*-butoxy; and

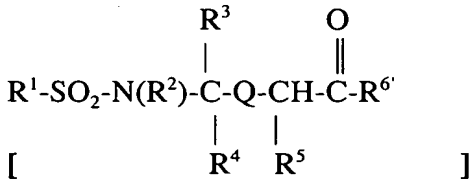
G.] when R^1 is *p*-methylphenyl, R^2 and R^3 are joined together with the nitrogen atom pendent to R^2 and the carbon atom pendent to R^3 to form a pyrrolidinyl ring, R^4 is methyl, R^5 is *p*-hydroxybenzyl then R^6 is not *t*-butoxy.

Claims 5 and 6 have been canceled.

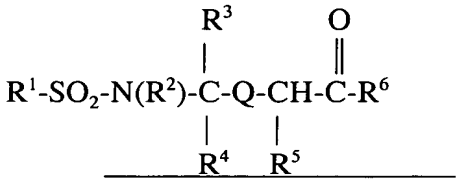
7. (Amended) The compound according to [Claim 6] Claims 1 or 2 wherein R^2 and R^3 together with the nitrogen atom bound to R^2 substituent and the carbon bound to the R^3 substituent form a substituted heterocyclic ring.

Claims 8, 9, 11 and 14 have been canceled.

16. (Amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



[



]

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

[R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R^2 does not form a heterocyclic group with R^1,] R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 [can] form a heterocyclic or a substituted heterocyclic group;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl[, and, when R^3 does not form a heterocyclic

group with R^2, then R^3 and R^4 together with the carbon atom to which they are attached can form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic group];

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is $=CH-X$ then (H) is removed from the formula and X is not hydroxyl;

R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), hydroxyl, amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, [and] or substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic [and] or substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

[and] or pharmaceutically acceptable salts thereof

with the [following provisos] proviso that

[A. when R^1 is *o*-carboxymethylphenyl, R^2 is hydrogen, R^3 is methyl, R^4 is methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

B. when R^1 and R^2 are joined to form a benzoisothiazolone heterocyclic ring, R^3 is methyl, R^4 is methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

C. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl or cyclohexyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not ethoxy;

D. when R^1 is benzyl, R^2, R^3 and R^4 are methyl, R^5 is *p*-hydroxybenzyl and Q is -C(O)NH-, then R^6 is not *t*-butoxy;

E. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl or cyclohexyl, R^5 is *p*-[*N,N*-(dimethylamino)carbonyloxy]benzyl and Q is -C(O)NH-, then R^6 is not *t*-butoxy;

F. when R^1 is benzyl, R^2, R^3 and R^4 are methyl, R^5 is *p*-[*N,N*-(dimethylamino)carbonyloxy]benzyl and Q is -C(O)NH-, then R^6 is not *t*-butoxy; and

G.] when R^1 is *p*-methylphenyl, R^2 and R^3 are joined together with the nitrogen atom pendent to R^2 and the carbon atom pendent to R^3 to form a pyrrolidinyl ring, R^4 is methyl, R^5 is *p*-hydroxybenzyl then [R^6] $\underline{R^{6'}}$ is not *t*-butoxy;

[H. when R^1 and R^2 are joined together with the SO_2 and nitrogen atom to which they are attached respectively to form a benzoisothiazolone heterocyclic ring, R^3 is methyl, R^4 is methyl, R^6 is hydroxyl, and Q is -C(O)NH- then R^5 is not benzyl;

I. when R^1 is *p*-methylphenyl, R^2 is hydrogen, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclohexyl, R^6 is hydroxyl, Q is -C(O)NH-, then R^5 is not benzyl; and

J. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl, R^6 is hydroxyl, Q is $-C(O)N(CH_3)-$, then R^5 is not benzyl].

18. (Amended) The method according to Claim 17 wherein said inflammatory disease is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes [(including acute juvenile onset diabetis)], inflammatory bowel disease [(including ulcerative colitis and Crohn's disease)], multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, [stroke, and other] cerebral traumas, nephritis, retinitis, atopic dermatitis,

psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.